

PATENT COOPERATION TREATY

PCT

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| REC'D | 19 FEB 2007 |
| WIPO | PCT |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|--|---|---|
| Applicant's or agent's file reference ALTUS/004PCT | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/US03/41545 | International filing date (<i>day/month/year</i>) 31 December 2003 (31.12.2003) | Priority date (<i>day/month/year</i>) 31 December 2002 (31.12.2002) |
| International Patent Classification (IPC) or national classification and IPC IPC: A61K 38/27(2006.01);C07K 14/61(2006.01) USPC: 530/399,418;514/12 | | |
| Applicant ALTUS BIOLOGICS INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 30 July 2004 (30.07.2004) | Date of completion of this report 18 January 2007 (18.01.2007) |
| Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201 | Authorized officer  Suzanne M. Noakes, Ph.D. Telephone No. 571-272-1600 |

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/41545

I. Basis of the report1. With regard to the elements of the international application:^{*}

the international application as originally filed.



the description:

pages 1-80 as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____.

the claims:

pages 81-93, as originally filedpages NONE, as amended (together with any statement) under Article 19pages NONE, filed with the demandpages NONE, filed with the letter of _____.

the drawings:

pages 1-21 as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____.

the sequence listing part of the description:

pages NONE, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:



the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).



the language of publication of the international application (under Rule 48.3(b)).



the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:



contained in the international application in printed form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:the description, pages NONEthe claims, Nos. NONEthe drawings, sheets/fig NONE5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).^{**}

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).
 ** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- the entire international application,
 claims Nos. 23-71

because:

- the said international application, or the said claim Nos. 23-71 relate to the following subject matter which does not require international preliminary examination (*specify*):

Said claims were no searched in Chapter 1 due to lack of unity and no additional fees were paid for the groups in which they were divided.

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 10,28-32 and 66-70 are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for said claims Nos. 23-71

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
 the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/41545

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- all parts.
- the parts relating to claims Nos. 1-9 and 11-22

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/41545**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

| | | |
|-------------------------------|--------------------------------|-----|
| Novelty (N) | Claims <u>5-9,11-16 and 18</u> | YES |
| | Claims <u>1-4,17 and 19-22</u> | NO |
| Inventive Step (IS) | Claims <u>5-9,11-16 and 18</u> | YES |
| | Claims <u>1-4,17 and 19-22</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-9 and 11-22</u> | YES |
| | Claims <u>NONE</u> | NO |

2. CITATIONS AND EXPLANATIONS

Claims 1-4, 17 and 19-22 lack novelty and inventive step under PCT Article 33(2) and (33) as being anticipated by Cunningham et al. (US 5,849,535).

The claims are drawn to a crystals of human growth hormone (calcium, monovalent, protamine or polyarginine) *or* a human growth hormone derivative (claims 1-4) and an excipient (claims 17 and 19-21) and wherein said composition is in a concentration of 0.1-100 mg/ml. The later half of the claim reads on soluble human growth hormone derivatives. Cunningham et al. teach soluble variants/derivatives of human growth hormone with several different amino acid substitutions (see claim 1) in a composition having an excipient/carrier of polyethylene glycol derivitized proteins (see claims 2-5). Furthermore, one of the pegylated hGH variants is in a composition of 10 mg/ml (see column 64, lines 23-25).

According to the International Search Authority, claims 1 and 17 also lack novelty and an inventive step as being anticipated by Junker et al. (6,117,984). Junker et al. teach divalent cation crystals of human growth hormone and compositions thereof (see claim 1). Calcium is a divalent cation and thus falls within the scope of Junker's claimed invention.

Thus, the recited claims lack novelty and an inventive step.

Claims 5-9 and 11-16 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest human growth hormone crystals that are calcium, monovalent cation, protamine or polyarginine crystals hGH, wherein the calcium crystals are novel because of the specific limitations of the preparations used to make said crystals and the required number of molecules per monomer.

Claims 1-9 and 11-22 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry. Specifically, hGH is well known to be used to treat various growth deficiencies so has direct industrial applicability in the biomedical industries.

----- NEW CITATIONS -----
US 5,849,535 A (CUNNINGHAM et al.) 15 December 1998, see claims 1-5, column 25 line 24 and column 64 lines 23-25.

PATENT COOPERATION TREATY

PCT

NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

| | | |
|-----------------------------------|---------------------------------------|--|
| International application No. | Applicant's or agent's file reference | Date of informal communication (day/month/year) |
| PCT/US03/41545 | ALTUS/004PCT | 30 January 2007 (30.01.2007) |
| Applicant ALTUS BIOLOGICS INC. | | |

| | | | | |
|--|---|---|--|---|
| <u>Communication</u> | <u>Participants</u> | <input type="checkbox"/> Identity checked | <input type="checkbox"/> authorization checked | <input type="checkbox"/> personally known |
| <input checked="" type="checkbox"/> by telephone | <input checked="" type="checkbox"/> Applicant: ALTUS BIOLOGICS INC. | | | |
| <input type="checkbox"/> personal | <input checked="" type="checkbox"/> Agent: James Haley | | | |
| | <input checked="" type="checkbox"/> Examiner(s): Suzanne Noakes | | | |

Summary of communication:

The Examiner invited Applicants to pay additional fees to be included in the Chapter II IPER. Three additional groups were searched in Chapter I (four total) and Mr. Haley indicated that he would like all of the same groups searched and prepared in Chapter II; he was informed the new fees would be required at \$600 per group since the demand was filed after Jan. 1, 2004. Mr. Haley authorized debiting of the authorized account. Additionally, the Examiner queried if it would be acceptable to do a 409 rather than a 408 written opinion. This was also acceptable to Mr. Haley.

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| <input type="checkbox"/> An extension of time limit is granted (Form PCT/IPEA/427). |
| <input checked="" type="checkbox"/> A copy of this note is being sent to the applicant with Form PCT/IPEA/429. |

PCT/IPEA/424.

| | |
|---|--|
| Name and mailing address of the IPEA/US | Authorized officer |
| Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201 | Suzanne M. Noakes, Ph.D.  Telephone No. 571-272-1600 |

Form PCT/IPEA/428 (July 1992)

UNITED STATES RECEIVING OFFICE (RO/US) FEE CODING AND RECORDING SHEET

ADDITIONAL SHEET

CERTIFICATION OF THE INTERNATIONAL APPLICATION

| INTERNATIONAL APPLICATION NUMBER | INTERNATIONAL FILING DATE |
|----------------------------------|---------------------------------|
| PCT US03/41845 | 31 DECEMBER 2003 - (31/12/2003) |
| APPLICANT (Name) | |

ALTUS BIOLOGICS

| PAYMENTS | | | | REFUNDS | | | |
|-------------------------------------|-------------|--|-------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|--|
| Payment on Filing | | | Deposit Account | Deposit Account | To Deposit Account | To Deposit Account | |
| Deposit Account | | | 06 1075 | | | | |
| | | | DATE: 14 DEC 2006 | DATE: | DATE: | DATE: | |
| <input type="checkbox"/> CASH/CHECK | | | <input type="checkbox"/> CASH/CHECK | <input type="checkbox"/> CASH/CHECK | <input type="checkbox"/> BY CHECK | <input type="checkbox"/> BY CHECK | |
| 160 | | | 16099180.00 | | | | |
| 151 | | | | | | | |
| 153 | | | | | | | |
| 800 | | | | | | | |
| 891 | | | | | | | |
| 892 | | | | | | | |
| | Total Paid: | | Total Paid: \$1800.00 | Total Paid: | Total Refunded: | Total Refunded: | |
| States included for 892: | 892: | | 892: | | | | |
| States included for 893: | 893: | | 893: | | | | |

Date Mailed:

| | | | | |
|------------------|---------------------|---------------------|---------------------|---------------------|
| RO/US Authorized | RO/US Authorization | RO/US Authorization | RO/US Authorization | RO/US Authorization |
| | | | | |

PCT RO/102(6) (U.S. VERSION)
(Rev. 10-82)

U.S. DEPARTMENT OF COMMERCE - Patent & Trademark

CHAPTER II
PCT TELEPHONE MEMORANDUM
FOR
LACK OF UNITY OF INVENTION



PCT No.: PCT/US03/41545

Examiner: Suzanne M. Noakes, Ph.D.

Attorney spoken to: Mr. James Haley

Date of call: 14 December 2006

- Amount of payment approved: \$1,800.00
 - Deposit account number to be charged: 06-1075
 - Attorney elected to pay for ALL additional inventions
 - Attorney elected to pay only for the additional inventions covered by
 - Group(s): 1-4
- encompassing --
- Claim(s): 1-22
 - Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention Group _____, covered by Claim(s) _____ has been examined.
 - Attorney was orally advised that there is no right to protest for any group not paid for.
 - Attorney was orally advised that any protest must be filed no later than 1 Month from the mailing of the Opinion (Form PCT/IPEA/408) or the Final Report (Form PCT/IPEA/409).

Time Limit For Filing A Protest

Applicant is hereby given 1 Month from the mailing date of this Opinion/Final Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 68.3, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

Itemized Summary of Claim Groupings:

Please See Continuation Sheet

Detailed Reasons For Holding Lack of Unity of Invention:

Please See Continuation Sheet

Note: A copy of this form must be attached to the Opinion/Final Report.

ATTACHMENT TO CHAPTER II PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

Itemized Summary of Claim Groupings:

- I. Claims 1, 7-9, 11, 13, 14 and 17-22, drawn to a calcium crystal of human growth hormone (hGH) or a hGH derivative.
- II. Claims 2, 5-9, 12, 15, 16 and 17-22, drawn to a monovalent crystal of human growth hormone (hGH) or a hGH derivative.
- III. Claim 3, 7-9 and 17-22, drawn to a protamine crystal of human growth hormone (hGH) or a hGH derivative.
- IV. Claims 4, 7-9 and 17-22, drawn to a polyarginine crystal of human growth hormone (hGH) or a hGH derivative.
- V. Claims 23-27, drawn to a method for treating a mammal having a disorder associated with human growth hormone deficiency with a calcium hGH crystal.
- VI. Claims 23-27, drawn to a method for treating a mammal having a disorder associated with human growth hormone deficiency with a monovalent cation hGH crystal.
- VII. Claims 23-27, drawn to a method for treating a mammal having a disorder associated with human growth hormone deficiency with a protamine hGH crystal.
- VIII. Claims 23-27, drawn to a method for treating a mammal having a disorder associated with human growth hormone deficiency with a polyarginine hGH crystal.
- XI. Claims 33-40, 45-65 and 71, drawn to a method of producing calcium hGH crystals.
- X. Claims 33-38, 41-65 and 71, drawn to a method of producing monovalent hGH crystals.
- XI. Claims 33-35, 45-47 and 53-55, drawn to a method of producing protamine hGH crystals.
- XII. Claims 33-35, 45-47 and 53-55, drawn to a method of producing polyarginine hGH crystals.

Detailed Reasons For Holding Lack of Unity of Invention:

The inventions listed as Groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the prior art recognizes the first named invention directed to calcium crystal of human growth hormone. Junker et al (US 6,117,984, issued 12 September 2000) discloses divalent cation crystals of human growth hormone (see claim 1, column 8). Because the number of divalent cation crystals is small and the members of the this groups are known to those in the art, this constitutes a disclosure of all members of this groups, including calcium crystals of human growth hormone. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to this cannot serve as a special technical feature because the expression "special technical features" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to, since the first claimed invention of calcium crystals of human growth hormone is known in the art, it cannot define over the art, and cannot serve to unite the claimed inventions. The technical features of each group are not shared, as decided by the inventions above, therefore, they are separate, multiple inventions as decided by PCT Rule 13.2.

Note: A copy of this form must be attached to the Opinion/Final Report.